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ECONOMIC ANALYSIS

Hospitalization Costs for Heart Failure in People with Type 2 Diabetes: Cost-Effectiveness of its Prevention Measured by a Simulated Preventive Treatment

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A B S T R A C T

Objectives: To estimate the cost-consequence of interventions to prevent hospitalizations for heart failure (HF) in people with type 2 diabetes. **Methods:** In HF events (63) from type 2 diabetes-related hospitalizations (N = 462) recorded in an Argentine hospital (March 2004–April 2005), we verified 1) the presence of one metabolic HF predictor (glycosylated hemoglobin [HbA1c] value) before hospitalization; and 2) in a simulation model, the resources needed for its prevention controlling such predictor during 6 months before and after the event. Sensitivity analysis of HF risk reduction, hospitalization cost, and cost of different treatments to achieve HbA1c 7% or less was performed with a Monte Carlo simulation (10,000 iterations). **Results:** HF represented 14% of hospitalizations, with a

44% rehospitalization rate for the same cause. Due to the total estimated cost for an HF hospitalization event was \$437.31, the prevention attained using our simulated treatment was \$2326.51. The number needed to treat to prevent an HF event under any of the proposed alternatives to reduce HbA1c would be 3.57 (95% confidence interval 2.00–16.67). The additional cost of the simulated treatment versus the real one oscillates between \$6423.91 and \$8455.68. **Conclusions:** HbA1c control to reduce the number of HF events would be economically beneficial for health care payers.

Keywords: cost analysis, diabetes, heart failure, prevention and control.

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Introduction

Heart failure (HF) represents a major public health concern because of its continuous incidence rise, hospitalization rate, and care costs. The United States has approximately 670,000 new HF cases per year in persons older than age 45 years [1,2] and its hospitalization rate has tripled between 1979 and 2004, partly due to the aging population and the efficiency of cardiovascular therapy [3]; the estimated HF cost burden in the United States in 2009 was \$37.2 billion [2].

The Framingham study established that a clinical history of diabetes was independently associated with risk of developing HF [4]. More recent studies [5] have reported higher annual incidences of HF in the diabetic population. Further, the Heart and Estrogen/Progestin Replacement Study demonstrated that diabetes was the strongest independent risk factor for HF development (adjusted hazard ratio 3.1) [6]. In people with diabetes, glycosylated hemoglobin (HbA1c) value is associated with HF

risk [7–9]. In a cohort study of 48,858 adult patients with predominantly type 2 diabetes, Iribarren et al. [7] showed that each 1% increase in HbA1c was associated with an 8% increased risk of HF hospitalization or death, even after adjusting for demographics, medical history, medications, and other risk factors. In the Atherosclerosis Risk in Communities study [9], the risk of HF also increased proportionally with HbA1c among people with diabetes and no evidence of previous HF [9].

Despite this strong evidence on the relationship between HF and HbA1c levels, the latter are above target values in most patients worldwide, including Argentina, [10,11]. Therefore, many HF events could be prevented in people with diabetes by improving their metabolic control, with the consequent beneficial effect for patients and the health care system.

To test this hypothesis, we carried out a cost-consequence study comparing the cost of HF events in people with type 2 diabetes with that of a simulated intensive preventive treatment of hyperglycemia.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Methods

To study the simulated cost of early intensive metabolic control to prevent hospitalization events caused by HF episodes in people with type 2 diabetes we adopted the following data collection scheme: we recorded all the hospitalization events of people with type 2 diabetes at the Hospital Privado de Comunidad (HPC), Mar del Plata, Argentina, from March 2004 to April 2005; thereafter, we identified those with HF events (International Classification of Diseases, Ninth Revision code 428), and evaluated their clinical and metabolic state. HbA1c levels (HF event predictor) and resource utilization rates during hospitalization were also recorded 6 months before and after the event. Diabetes and associated obesity, hypertension, and dyslipidemia were identified using American Diabetes Association criteria [12].

According to Stratton et al. [8], we defined an HF event as preventable when the patient had no HF antecedents and a HbA1c value greater than 7%; the benefits of our intervention were also measured according to these authors: a 14% HF risk reduction for each 1% decrease in HbA1c independent of the treatment used to attain such value.

The study was implemented according to the Good Clinical Practice Recommendations (International Harmonization Conference), the 5330/97 regulation of the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, National Law 25.326 of Personal Data Protection, and the ethical Helsinki Declaration guidelines. The study protocol was approved by the HPC Ethics Committee.

Simulated pharmacologic interventions to control HbA1c

Before the HF event

Alternative I [12]: 1) Metformin (2,500 mg/day) plus glibenclamide (15 mg/day) in patients treated with both drugs; 2) metformin (850 mg/day) plus glibenclamide (10 mg/day) in patients without previous drug treatment; and 3) insulin (40 IU/day) in patients previously treated with insulin. Alternative II [12]: 1) Metformin (2,500 mg/day) plus glibenclamide (15 mg/day) in patients treated or not with both drugs, and 2) insulin (40 IU/day) in patients previously treated with insulin. Alternative III (as in the United Kingdom Prospective Diabetes Study [13]): Metformin (2,500 mg/day) in 32% of cases and metformin (1,700 mg/day) plus glibenclamide (10 mg/day) in the remaining 68% of patients.

Self-monitoring blood glucose

Because there is no general agreement on the appropriate number of strips, we established the following arbitrary number for strip use: 1) 40 to 72 strips/patient/month for insulin-treated patients; and 2) 24 strips/patient/month for those treated with oral agents and with no previous strip consumption. The glucometer cost was not included in the estimation because in general is provided free of charge.

After the HF event

Insulin administration (daily 40 IU/day) in all cases and 72 strips/patient/month.

Costs

We considered direct medical costs from the health payers' perspective. Because we do not have the real cost of an acute event, we adopted the values of the largest social security health care payer (Instituto de Obra Médico Asistencial) in hospitals with similar characteristics to the HPC. Ambulatory care costs (doctor visits, laboratory tests, and other medical practices) were estimated using the National Care Nomenclature Values.

Pharmacotherapy cost was based on a microosting approach using a mean unit retail price per milligram of each drug or per insulin units included in the study (recorded or proposed), and the corresponding daily dose (recorded or proposed). With these data, we estimated the mean daily cost for each drug for a 6-month period before and after the HF event.

We compared thereafter the cost of the proposed treatment minus the real treatment versus the cost of the hospitalization events minus that of the prevented events (including ambulatory care costs before and after such event).

Costs were calculated on Argentinean pesos and converted to US dollars at the average official exchange rate for the period March 2004 to April 2005 (\$1 = 2.94 Argentinean pesos).

Sensitivity analysis

The probabilistic sensitivity analysis included: 1) the total cost of the HF event; 2) the unitary cost of drugs and strips; and 3) the relative risk reduction (percentage) to develop a HF event. A Monte Carlo simulation was carried out (10,000 iterations), assuming 1) a uniform distribution (minimum = \$246.26; maximum = \$724.49) based on pre-established values for HF events from many possible scenarios defined by Instituto de Obra Médico Asistencial; 2) self-generated probability distributions using monthly observations of mean price per milligram (for each drug either used or proposed) and mean price per unit (for each strip) in the Argentine pharmaceutical market at six months before and after the event; and 3) a normal distribution with a mean of 14% and a standard deviation of 2% for the HF relative risk reduction from hyperglycemia treatment that allowed us to achieve the 95% confidence interval reported by Stratton et al. [8]. We used Monte Carlo iterations to calculate Pearson's coefficient to assess the level of association between these assumptions and the result (additional total cost for each of the alternatives considered).

Also, we assumed that 1) the antihyperglycemic therapy implemented could reduce the relative risk for non fatal HF with a comparable effectiveness to that recorded in the United Kingdom Prospective Diabetes Study [8,14], despite our population hospitalized for HF was older than that of the United Kingdom Prospective Diabetes Study; and 2) the decreased relative risk for HF would be linear; that is, a 14% risk decrease by each 1% HbA1c decrease.

All calculations were performed in MS-Excel 11.0 (Microsoft Corp., Redmond, WA) with add-on Crystal Ball Trial Version (Decisioneering (R), Inc., Denver, CO).

Results

Out of a total of 462 hospitalized patients with type 2 diabetes, 38% of admissions were related to cardiovascular disease, HF being the most frequent cause (14%); 44% of the HF events were rehospitalized for the same cause. Forty-nine percent were women, with a mean age of 77.1 ± 8.4 years; 80% were obese (body mass index > 30); 77% had hypertension; and 71% had hypercholesterolemia. HbA1c levels were between 7.6% and 8.6%. Thirty percent of the population had microangiopathic complications (e.g., neuropathy, retinopathy, or nephropathy) and 29% had macroangiopathic signs/events (e.g., acute myocardial infarction, stroke, or lower-limb claudication) (Table 1 in Supplemental Materials found at: [doi:10.1016/j.jval.2011.05.018](https://doi.org/10.1016/j.jval.2011.05.018)). Sixteen out of the total 63 HF events were preventable by tight control of HbA1c (criteria mentioned above).

Thirty-one percent of the patients hospitalized for HF events and with HbA1c of 7% or greater ($n = 16$) received no antidiabetic drug treatment before the event; 55% of those treated received oral monotherapy (metformin or glibenclamide), 18% received combined therapy, and the remaining 27% was treated with insulin. After the event, 50% of patients received no antidiabetic treatment and among those treated, 37% received monotherapy (19% some

oral agent and 18% insulin), whereas 12% received combined oral therapy (Table 2 in Supplemental Materials found at: [doi:10.1016/j.jval.2011.05.018](https://doi.org/10.1016/j.jval.2011.05.018)).

As mentioned, 28% of the HF events would be preventable (4.48 over 16 HF events) with the antihyperglycemic pharmacologic interventions proposed; a proportional number of rehospitalizations for HF events would be also avoided (0.84 cases). Because the total estimated cost for a HF hospitalization event was \$437.31, the prevention using our simulated treatment would be \$2,326.51. The number needed to treat to prevent an HF event with any of the pharmacologic options proposed to reduce HbA1c would be 3.57 (95% confidence interval 2.00–16.67).

The total cost of the simulated treatments was (in US dollars): Alternative I = \$13,615.09, Alternative II = \$14,079.34, and Alternative III = \$12,047.58; the real treatment was \$3297.16. Consequently, the additional costs were \$7991.42, \$8455.68 and \$6423.91 for Alternatives I, II, and III, respectively (see Table 3 in Supplemental Materials found at: [doi:10.1016/j.jval.2011.05.018](https://doi.org/10.1016/j.jval.2011.05.018)).

According to the pre-event treatment costs and with an arbitrary decision threshold of \$510.20 for the net per capita additional cost of the simulated treatment, the probability to surpass would be 36%, 52%, and 2.3% for Alternatives I, II, and III, respectively. Such cost variation could be ascribed to the total minimal/maximal cost of the event (Pearson's correlation in each of the alternatives considered ranged from -0.65 to -0.71), strips (Pearson's correlation 0.49 to 0.52), insulin (Pearson's correlation 0.32 to 0.40) and the percent reduction of HF risk (Pearson's correlation -0.31 to -0.33). In all cases, the correlation coefficients had the expected sign and significance for the confidence level used (95%).

Discussion

As already reported, we found that cardiovascular disease was the main cause of hospitalization, with a particularly high frequency of HF [15]. Based on the reported relationship between HbA1c and HF [5,7–9], we tested the simulated cost-consequence of improving HbA1c levels to prevent HF hospitalization events in people with type 2 diabetes. Our data showed that the probability to surpass an arbitrary decision threshold of \$510.20 for the net per capita additional cost of the simulated treatment was 36%, 52%, and 2.3% for the medium, highest, and lowest alternative treatment costs, respectively. Such variation would depend on the cost of the event, the strips, and the insulin treatment, as well as on the percent reduction of HF risk. These results confirm our working hypothesis that prevention of HF events in people with type 2 diabetes has a reasonable and affordable cost for payers. It should be noted that the cost of the intensive hyperglycemia treatment was high because we applied the traditional insulin treatment after the event, regardless of reported evidence showing that metformin could also be used in these patients [16]. The use of metformin rather than insulin would decrease significantly the preventive treatment cost. In addition, the low number needed to treat value plays in favor of its applicability in settings similar to the one currently described. Beyond this economic achievement, prevention of HF hospitalization events could also decrease their high recorded mortality rate (23%).

In our sample, 33% of the patients hospitalized for HF events and with HbA1c 7% or greater did not receive antidiabetic drug treatment before the event and more than half of them received a single drug. Comparable undertreatment behavior was observed after the event. Our results promote a more proactive treatment attitude.

Our conclusions are in line with the proposal of Karter et al. [17] about the convenience for health financing entities to provide coverage for preventive strategies now instead of complete coverage for recovery/rehabilitation strategies in the future. In Argentina, the Health Ministry provision of economic incentives to entities of

the Social Security subsector that include preventive strategies in their care programs for chronic diseases, play also in favor of this concept. This policy would be particularly important in developing countries, where the expected rise in the prevalence of diseases such as type 2 diabetes will imply an increased demand of care both in the short and long term [11,18].

As with most simulation studies, our own has some limitations, namely 1) we had no direct information on glycemic self-monitoring performance; and 2) we assumed a linear efficacy relationship between risk factor reduction and HF prevention, despite many authors have shown the appropriateness of using Weibull distributions and accelerated failure time equations to treat these relationships [7,19,20]. Nonetheless, using the Economic Assessment of Glycemic Control and Long-Term Effects of Diabetes model hazard ratios [14] for nonfatal HF, we found high and similar goodness of fit between a logarithmic ($R^2 = 0.998$ for hyperglycaemia relative risk reduction) and a linear tendency ($R^2 = 0.927$) to adjust hazard ratio reductions from different HbA1c values (7%–11%) (data not shown; it is available from the authors on request). Thus, although not precisely estimated, our results would still be valid, conservative, and suitable for evidence-based decision making.

Conclusions

Considering that no similar data have been previously reported, our results show for the first time that intensive hyperglycemia treatment to decrease the number of hospitalizations for HF events in people with type 2 diabetes would have a favorable cost-consequence ratio. Thus, we believe it is important to identify inadequate HbA1c values in people with type 2 diabetes and treat them to reach values within target, as recommended by international guidelines. This preventive policy would simultaneously decrease cardiovascular complications requiring high-cost hospitalization and rehospitalization, with the consequent optimization on the use of economic resources.

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Supplemental Materials

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REFERENCES

- [1] Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. *J Am Coll Cardiol* 2010; 55:283–93.
- [2] Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update. A report from the American Heart Association

- Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:e21–181.
- [3] Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol* 2008;52:428–34.
 - [4] Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34.
 - [5] Nichols GA, Gullion CM, Koro CE, et al. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879–84.
 - [6] Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation* 2004;110:1424–30.
 - [7] Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668–73.
 - [8] Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
 - [9] Pazin-Filho A, Kottgen A, Bertoni AG, et al. HbA1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia* 2008;51:2197–204.
 - [10] Chan JC, Gagliardino JJ, Baik SH, et al. The IDMPs Investigators. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). *Diabetes Care* 2009;32:227–33.
 - [11] Gagliardino JJ, de la Hera M, Siri F; Grupo de Investigación de la Red QUALIDIAB. Evaluación de la calidad de la asistencia al paciente diabético en América Latina. *Rev Panam Salud Pública* 2001;10:309–17.
 - [12] American Diabetes Association: clinical practice recommendations. *Diabetes Care* 2002;25(Suppl.):S1–147.
 - [13] Turner RC, Frighi CC, Holman RR. Glycemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005–12.
 - [14] Mueller E, Maxion-Bergemann S, Gultyaev D, et al. Development and validation of the Economic Assessment of Glycemic Control and Long-Term Effects of Diabetes (EAGLE) model. *Diabetes Technol Ther* 2006;8:219–36.
 - [15] Carr AA, Kowey PR, Devereux RB, et al. Hospitalizations for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies. *Am J Cardiol* 2005;96:1530–6.
 - [16] Tahrani AA, Varughese GI, Scarpello JH, Hanna FWF. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *BMJ* 2007;335:508–12.
 - [17] Karter A, Stevens M, Herman WH, et al. Out-of-pocket costs and diabetes prevention services: the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care* 2003;26:2294–9.
 - [18] Primera Encuesta Nacional de Factores de Riesgo. Ministerio de Salud de la Nación. Available from: <http://www.msal.gov.ar/htm/Site/enfr/index.asp>. [Accessed June 23, 2006].
 - [19] Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2003;138:10–6.
 - [20] Clarke PM, Gray AM, Briggs A, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) outcomes model (UKPDS 68). *Diabetologia* 2004;47:1747–59.